In the ABSTRACT

Insert the abstract submitted herewith on a separate sheet.

REMARKS

Claims 1-5, 7, 8, 11 and 22-26 are pending in the application. Claims 1 to 5, 7 to 8 and 11 have been amended to relate to a process of producing a sterile foam rather than a formulation. There is support for this amendment in former Claim 21 as filed and at page 8, lines 28 to page 9 line 22 of the specification as filed. The precipitant is now specified as being calcium citrate or a calcium ion releasing water soluble glass. There is support for this amendment at page 3, lines 27 to 31 and page 9, lines 31 to 35 of the specification as filed.

The dependencies of Claims 7, 11, 22 and 23 have been amended to take into account the deletion of Claims 6, 9, 10 and 12 to 21. New Claims 25 and 26 have been added. New Claim 25 is directed to the washing option set forth as step d) in former Claim 21. New Claim 26 relates to a foam obtained in accordance with the process as claimed in Claim 1. No new matter has been added.

I. Specification

The Examiner indicated that the application does not contain an abstract of the disclosure. An abstract of the invention is included herewith on a separate sheet.

II. RESPONSE TO 35 U.S.C. 112 REJECTION

The term "slow release" has been deleted from Claim 1.

Claim 1 has been amended to delete the terms "therefore" and "thereof".

Claim 1 has been amended to delete the term "foamed form of the."

The phrases "or derivatives" in Claim 3 and "derivatives ... thereof" in Claim 4 have been deleted. Claims 15 and 16 have been cancelled.

Claim 3 rather than Claim 4 now specifies that the gelling agent may be carageenan gel. Claim 16 has been cancelled.

The term "or the like" has been deleted from Claim 8, and Claim 20 has been cancelled.

Claims 6, 13 and 18 have been cancelled and the objections set forth in paragraphs (vi) and (vii) of the Office Action have thus been overcome.

Thus, Applicant submits that following entry of the above-mentioned amendments, all objections under 35 U.S.C. 112 have been overcome.

III. REJECTION OF CLAIMS 1, 3 TO 9, 12 TO 13 AND 15 TO 20 UNDER 35 U.S.C. 102

Claim 1 as amended relates to a method of producing a sterile foam wherein the foam or foamed formulation is treated with a precipitant being calcium citrate or a calcium ion releasing water soluble glass. This method was the subject of former Claim 21, now cancelled. Whilst it has been noted that the Examiner did not raise any objections under 35 U.S.C. 102 against former Claim 21, the following remarks are provided

regarding the novelty of the invention defined by amended claims 1.

Bakis et al. (U.S. Patent No. 5,851,461) discloses a method of producing a sterile foam, wherein after the foam is formed, the dried foam is contacted with cross-linking di- or tri-valent cations (see column 2, lines 46 to 58). The di- or tri-valent cations may be Ca^{2+}, Fe^{2+} or Fe^{3+}. Alternatively the cations may be added to the foam in the form of a carbonate or a hydrogen carbonate salt (see column 4, lines 29 to 48). There is no teaching or suggestion in Bakis et al. that calcium citrate or calcium ion releasing water soluble glass may be used to stabilise the gelling agent as specified in Claim 1 as amended.

Claim 1 as amended specifies that the precipitant is combined with the gelling agent during the foaming of the gelling agent, and that the foamed formulation is then immersed in precipitant. Bakis et al. teach that the di- or tri-valent cations are added to a dried foam (see column 2, lines 46 to 58). The di- or tri-valent cations are washed or sprayed on the foam (see column 4, lines 30-32), but Bakis et al. does not teach or suggest that the precipitant may be combined with the gelling agent before or during the foaming of the gelling agent, and thus before the foam is produced.

Furthermore there is no teaching or suggestion that the foams of Bakis et al. may be sterilised through the use of gamma-irradiation or ethylene oxide as now specified in Claim 1 as amended.

Comer et al. (US Patent No. 3,962,482) describes an edible dessert gel in contrast to the present invention, which

relates to a method of producing a sterile foam. Comer and the present invention are thús in different fields of technology. Comer et al. make no teaching or suggestion that the formulations described therein may be utilized in medical of veterinary fields.

Furthermore there is no teaching or suggestion that the formulations of Comer may be sterilised through exposure to gamma-irradiation or ethylene oxide.

Bannert (US Patent No. 5,147,648) discloses gels having improved adhesion properties (see column 1, lines 9 to 11), in contrast to the present invention which relates to a method of producing a foam. Bannert does not teach a foaming step as specified in Claim 1 as amended. The gels disclosed in Bannert may comprise alginic acid and a calcium salt such as a citrate (see column 2, lines 12 to 24).

There is no teaching or suggestion that the gels of Bannert may be sterilised by exposure to gamma-irradiation or ethylene oxide. Furthermore it is an essential feature of Bannert that the gels disclosed therein are formed *in situ* on the mucosa (see column 1, line 52 to column 2, line 2). The gel could not be sterilised by exposure to gamma-irradiation or ethylene oxide whilst on the mucosa as this would lead to direct exposure of the human body to gamma-irradiation which would be harmful.

Cole et al. (US Patent No. 5,089,606) describes a foam containing a polysaccharide, preferably alginate (see column 5, lines 31 to 53 and column 6, lines 5 to 9), water insoluble di- or tri-valent metal salts, preferably calcium carbonate, calcium phosphate dibasic, barium carbonate or zinc carbonate

(see column 6, lines 31 to 35) and an effervescent compound. The composition of Cole et al. becomes a foam through the effervescing of the effervescent compound (see column 11, lines 4 to 7).

Garbe (European Patent No. 0390254) discloses a method of preparing non-foamed gels (see column 2, lines 60 to 63). The method comprises the steps of mixing a di- or tri-valent metal salt in an aqueous solution of polysaccharide with a water soluble acid (see column 3, lines 8 to 25). The polysaccharide is preferably sodium alginate (see column 3, line 62 to column 4, line 2). Preferably the metal salt is calcium carbonate, calcium phosphate dibasic, barium carbonate or zinc carbonate (see column 4, lines 11 to 15).

There is no teaching or suggestion that the compositions of Cole et al. or Garbe may contain calcium citrate or calcium ion releasing water soluble glass as specified in Claim 1 as amended. Furthermore there is no teaching that the formulations of either of these documents may be sterilised by exposure to gamma-irradiation or ethylene oxide.
Cole et al. and Garbe also state that it is conventional to add cross-linking calcium ions to gels (see column 1, lines 37 to 41 of Cole et al. and Garbe). Neither of these documents teach that it is conventional to add such substances to foams, however.

Gilchrist et al (WO 96/17595) describes a foam comprising a gelling agent and a calcium ion releasing water soluble glass. It does not teach immersing the foamed formulation within a precipitant, sterilising the foam (as opposed to a gel formulation) though exposure to gamma-irradiation or ethylene oxide.

Neumann (US 4,086,331) teaches a gelatin-based composition which is stabilised by the presence of water soluble ferous salt. It does not disclose that the foam produced might be sterile, nor the use of calcium citrate or a calcium ion releasing agent as a precipitant or stabiliser. Lastly, Neumann does not teach immersing the foamed formulation in a bath of precipitant.

Accordingly, for the reasons explained above, Applicants assert that Claim 1 is patentable over the cited references. Further, claims 2-5, 7, 8, 11, and 22-26 depend from claim 1 and therefore include all the features of claim 1. Accordingly, Applicants assert that these claims are patentable over the cited art at least for the same reasons described above with regard to claim 1.

IV. REJECTION OF CLAIMS 1 to 24 UNDER 35 U.S.C.103

The Examiner considers that Claims 1 to 24 are unpatentable over Bakis et al. in view of Bannert, Cole et al. and Gilchrist et al.

There is no teaching or suggestion that calcium citrate or calcium ion releasing water soluble glass may be added to the foams produced according to Bakis et al. Furthermore Bakis et al. do not teach that a precipitant may be added to the gelling agent during foaming, before curing as specified in Claim 1 as amended. Bakis et al. teach that di- or tri-valent cations are added to the dried foam (see column 2, lines 46 to 58). There is no teaching or suggestion that the foams formed according to Bakis et al. may be sterilised by exposure to gamma-irradiation or ethylene oxide.

Bannert relates to gels and as such relates to a different field of technology from the present invention. The present invention relates to a method of producing a sterile foam. Bannert discloses that calcium salts may be added to the gel disclosed therein to form cross-linking (see column 2, lines 15 to 24). Bannert teaches that components of the finished gel are applied to the mucosa separately and only mixed after application to the mucosa (see column 1, line 59 to column 2, line 2). Bannert does not teach or suggest a foaming step, or that the final formulation may be immersed in a bath of precipitant as specified in Claim 1 as amended.

Furthermore Bannert makes no teaching or suggestion that the formulation described therein may be sterilised by exposure to gamma-irradiation or ethylene oxide.

Cole et al. relates to a polysaccharide hydrogel foam which may contain alginate, a di- or tri-valent metal salt and an effervescent compound. There is no teaching or suggestion that calcium citrate or calcium ion releasing water soluble glass may be added to the foam. Furthermore Cole et al. make no teaching or suggestion that the foam disclosed therein may be sterilised through exposure to gamma-irradiation or ethylene oxide.

Gilchrist et al. (WO/ 96/17595) relates to a foamable formulation which may comprise a calcium ion releasing water soluble glass (see page 10, lines 5 to 17). Gilchrist et al. states that the formulation may be a gel, and that the gel may be sterilised by gamma-irradiation (see page 5, line 28 to page 6 line 12). A Declaration from Eilidh Trainer née Gilchrist is submitted herewith. Eilidh Trainer is one of the

inventors of the present invention and of the Gilchrist et al. invention. The Declaration submitted herewith contains experimental evidence showing that the foams formed according to Gilchrist et al. cannot withstand exposure to gamma radiation or ethylene oxide without collapsing or being degraded. The data submitted in the Declaration also evidences that the foams of the present invention can withstand exposure to gamma radiation and ethylene oxide whilst maintaining their structure and good absorbtion capabilities.

The Examiner considers that it would have been obvious to one of ordinary skill in the art at the time the invention was made, to have modified the invention of Bakis et al. using the teachings of Bannert because Bakis et al. and Bannert both teach hydrogel foams comprised of polysaccharids and di-or or tri-valent salts. Applicant strongly disputes this. Bannert discloses a gel not a foam (see column 1, lines 48 to 51) and as such relates to a different field of technology. There would have been no motivation at the time of the invention to combine these documents as they are in different fields. The Examiner considers that both Bakis et al. and Bannert teach alginate as a polysaccharide and calcium salts as di- or tri-valent salts. Applicant submits that Bakis et al. makes no teaching or suggestion that the calcium salts may be calcium citrate or calcium ion releasing water soluble glass as specified in Claim 1 as amended. The Examiner asserts that both Bakis et al. and Bannert teach gels for medical use. As described above Bakis et al. relates to a foam, whereas Bannert relates to a gel. The Examiner considers that Bannert et al. teaches that the separation of the gelling agent and the precipitant and the subsequent application of each component onto the mucosa results in a gel that more strongly

adheres to the mucosa. The Applicant agrees that the application of components of the gel to the mucosa and the *in situ* formation of the gel on the mucosa is an essential feature of Bannert (see column 1, line 59 to column 2, line 2). As such it would not be safe to expose the applied gel to gamma-irradiation or ethylene oxide, as this would lead to direct exposure of the human or animal body. Bannert thus teaches away from the present invention. Furthermore Bannert makes no teaching or suggestion that the formulation disclosed therein may be sterilised by exposure to gamma-irradiation or ethylene oxide.

The Examiner also considers it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of the above-combined Bannert and Bakis et al. references using the teachings of Cole et al., as both the combined references and Cole et al. teach hydrogel foams comprised of polysaccharide and di- or trivalent salts. As stated above Bannert relates to a gel rather than a foam. The Examiner considers that both the combined Bannert and Bakis et al references and Cole et al. teach alginate as a polysaccaride and calcium salts as di or trivalent salts. None of these documents however teach a foam comprising calcium citrate or a calcium ion releasing water soluble glass. The Examiner considers both the Bannert and Bakis et al. references and Cole et al. teach gels for medical use and both teach separation of the gelling agent (polysaccharide) from the precipitant. Formation of the gel of Bannert *in situ* is an essential feature of the invention described therein. This above makes exposure of the gel to gamma-irradiation or ethylene oxide unsafe. Cole et al. also teach away from exposure of the foam described therein to gamma-irradiation or ethylene oxide as the formulation is

preferably formed *in situ* (see column 4, lines 35 to 37). It would not be safe to directly expose humans of animals to gamma-irradiation or ethylene oxide. A combination of Bannert, Bakis et al. and Cole et al. would thus not result in the invention of Claim 1 as amended. Furthermore there would have been no motivation at the time of the invention for one skilled in the art to make such a combination.

The Examiner states that Cole et al. teach the addition of calcium carbonate causes formation of a stable hydrogel foam. The addition of calcium carbonate is no longer included in Claim 1 as amended. The Examiner asserts it would have been obvious to have modified the combined references using the teachings of Gilchrist et al. and obtain a process of sterilising the gel comprising gamma-irradiation. The Trainer Declaration evidences that foams according to Gilchrist et al. cannot withstand gamma-irradiation. There is no teaching or suggestion that the foams disclosed therein may be sterilised through exposure to ethylene oxide. Thus, the combination of the Bannert, Bakis et al. and Cole et al. references with Gilchrist et al. does not provide the invention of Claim 1 as amended.

In summary none of the prior art documents cited make any teaching or suggestion that the formulations described therein may be treated with a precipitant before or during foaming and immersed in precipitant once foamed. None of the prior art documents cited teaches or suggests that the foamed formulation may be sterilised by exposure to gamma-radiation or ethylene oxide except for Gilchrist et al., which describes the sterilisation of a gel formulation prior to foaming. Evidence has been submitted that the foams of Gilchrist et al. are not suitable for exposure to gamma-radiation as they

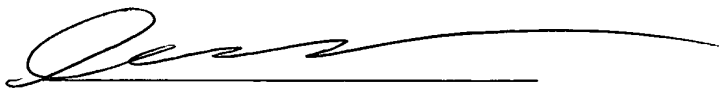
breakdown and deteriorate and that foams exposed to ethylene oxide are of the lowest standard and present substantially diminished absorption. Bannert and Cole et al. teach away from a sterilisation step after formation of the formulations described therein as the formulations are formed *in situ*. As such Applicant submits that the present Application is therefore nonobvious over the prior art documents cited.

New Claim 25 relates to a foam obtained by the process of the invention. This product is novel over the cited prior art as it is able to withstand sterilisation by exposure to gamma-irradiation or ethylene oxide. As evidenced in Eilidh Gilchrist's declaration enclosed herewith, prior art foams could not be sterilised in this way and maintain their structural integrity or their absorbtion capability.

It is therefore believed that the Examiner's rejections under 35 USC 102, 103 and 112 have been overcome by the amendment of the Claims and issuance of the Patent is therefore solicited.

Respectfully submitted,

TOM GILCHRIST, et al.

BY: 

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APPENDIX A - MARKED UP COPY OF THE CLAIMS

1. (Amended) A process of producing a sterile foam for medical or veterinary use, said process comprising the following steps:

   a) foaming a [A] physiologically acceptable formulation for application to a body as a foam, said formulation comprising a foamable gelling agent; [and a slow release precipitant therefor,]

   b) treating said foamed formulation with a precipitant wherein the precipitant is calcium citrate or a calcium ion releasing water soluble glass, and [wherein] said [slow release] precipitant is combined with said gelling agent before or during the foaming [thereof] of the gelling agent and stabilises the [foamed form of the] gelling agent[.];

   c) allowing the foam thus obtained to cure;

   d) immersing the foam in a bath of said precipitant;

   e) drying said treated foam; and

   f) sterilising said dried foam by exposure to gamma-irradiation or ethylene oxide.

2. (Amended) A [formulation] process as claimed in Claim 1, wherein said precipitant is packaged separately to said gelling agent prior to foaming.

3. (Twice Amended) A process [formulation] as claimed in Claim 1, wherein said gelling agent is alginate, carboxymethylcellulose, collagen, a polysaccharide, agar, a polyethylene oxide, a glycol metacrylate, carageenan gel, gelatin, a gum, or salt[s or derivatives] of any of these, or mixtures thereof.

4. (Amended) A process [formulation] as claimed in Claim 3 wherein said gelling agent is alginate, carboxymethyl-cellulose, [carageenan gel the derivatives or] salt[s] thereof, or mixtures thereof.

5. (Twice Amended) A process [formulation] as claimed in Claim 1, wherein said gelling agent has a molecular weight of from 10,000 to 200,000 kDa.

7. (Twice Amended) A process [formulation] as claimed in Claim 1, wherein said formulation further contains [containing] a foaming agent.

8. (Amended) A process [formulation] as claimed in Claim 7, wherein said foaming agent is cetrimide, lecithin, a soap, silicone, or a surfactant [or the like].

11. (Twice Amended) A process [formulation] as claimed in Claim 1, wherein said formulation further comprises [comprising] an organic acid in an amount of 0.5 g to 5.0 g per 100 g gelling agent.

22. (Amended) The process of Claim [21] 1, wherein said [treated] foam is washed in a de-ionised water/glycerine mixture prior to drying.

23. (Twice Amended) The process of Claim 1 [21] wherein the [treated] foam is oven dried at temperatures below 100°C.

24. (Twice Amended) The process of Claim 1 [21] wherein the foam is immersed in a bath of [calcium chloride or] calcium citrate solution as precipitant.